REMARKS

Claims 1-3, 5, 8-12, 14-19, and 21-31 are pending in the application, claim 26 has been cancelled by this amendment. Therefore, claims 1-3, 5, 8-12, 14-19, 21-25, and 27-31 are at issue.

The courteous interview granted by Examiner Patel to applicants' undersigned attorney on July 29, 2004 is hereby acknowledged with appreciation. During the interview the outstanding Office Action and claims were discussed in detail.

In the present Office Action, the examiner states that claims "19, 21-25, 29-31 if limited to compounds not overlapping with the rejections stated below, and related to invention of Group I would be novel." Examiner's Group I includes claims that are "drawn to compounds, composition, a method of use for claim 1 generic Formula: 'W-X1-C(=Y)-X2-Z, wherein W=6-membered monocyclic heterocycle with 1,4-diazine ring=Pyrazine; Y=O or S; Z=Aryl or phenyl." See Office Action of September 5, 2003, page 2. It also should be noted that in the Office Action of December 19, 2003, at page 4, that examiner stated that claimed compounds of Examiner's Group I have been examined in their entirety.

Applicants have amended the claims to conform in scope to the fully searched Examiner's Group I. Applicants note that the amendments do not narrow the scope of the invention and reserve the right to pursue withdrawn subject matter in one or more divisional applications. It is submitted that the compound claims are in condition for allowance. As stated in Amendment

"B," claims 4, 6, 13, and 20 were cancelled to conform the claims to the elected invention, not for reasons of patentability, without prejudice to filing continuing applications directed to the subject matter of these claims.

The examiner states that applicants' method claims are not limited to compounds of examiner's Group I and that some of the compounds recited in the method claims are not novel. First, the method claims have been amended to conform the compounds in scope with Examiner's Group I. The compounds recited in the method claims were amended in previous Amendment "B." The examiner's statement that the compounds in the method claims are not limited to examiner's Group I, therefore, is incorrect.

The examiner is correct, however, in stating that the methods recite compounds not encompassed by the compound claims. The compound claims recite novel compounds. The method claims recite a use of compounds that were not identified in any cited prior art document as Chk1 inhibitors. Applicants were the first to recognize that the compounds have an ability to inhibit Chk1. The method claims recite, therefore, these compounds because the claimed method using these compounds is itself novel in view of the cited prior art. Even if it may be argued that some of the compounds were known in the art, it is well accepted that a new use of known compounds may be patentable. The recitation of a new use for an old compound is well accepted.

In addition, the specification contains numerous examples showing (a) how Chk1 inhibitors can

be identified, and (b) that compounds recited in the method claims are capable of inhibiting Chk1. Applicants provided substantial data showing the efficacy of compounds having the claimed structure. It is not necessary to differentiate novel from known compounds with respect to these tests, and the test is itself not dependent upon whether a compound is or is not previously known in the art. Such protocols are easily performed by persons skilled in the art without undue experimentation.

Contrary to the examiner's contentions, the specification contains supporting evidence showing that the recited compounds perform in the claimed methods. Whether a compound is novel or known is irrelevant with respect to the *method* claims, what is relevant is whether use of the compounds (either novel or known) in the claimed method is novel and nonobvious. It is the *identity* of the compounds which perform the claimed method that is important. The novelty of the *compounds* is *not* at issue in the method claims.

The examiner objects to claims 1-3, 5, 8-12, and 14-18 as being improper for failing to further limit the subject matter of a previous claim. Applicants are confused by this objection. Claims 1 and 8 already *are* independent claims. Dependent claims 2, 3, 5, 9-12, and 14-18 each are already narrower than the claim from which they depend. Applicants respectfully submit that the objection is in error and should be withdrawn.

The examiner also states that a new use or function that is inherently present in the prior art

does not make the claim patentable. Pursuant to M.P.E.P. §2112.02, for such a rejection to be made, art must be cited such that the new use can be deemed inherent in that art. The present method claims recite compounds that inhibit Chk1. No art has been cited teaching or suggesting that the recited compounds were known for such a use, or that such a use would be inherent from that art. Accordingly, the examiner's statement is unsubstantiated and irrelevant with respect to the present claims. Applicants also submit that the examiner's statement with respect to the "use of different starting materials, whether novel or known" is irrelevant. The art does not teach or suggest using the recited compounds in the claimed methods.

Claims 19, 21-25, and 28-31 still stand rejected under 35 U.S.C. §112, second paragraph, for the reasons stated in the Office Action of December 19, 2003. This rejection was addressed in prior Amendment "B," and the examiner has failed to articulate why the previous rejection still stands, even though applicants have made amendments previously suggested by the examiner. Accordingly, applicants readdress the 35 U.S.C. §112, second paragraph, rejections. In particular, the examiner is directed to previously filed Amendment "B," from which the following is repeated verbatim.

> "The examiner stated that claims 19-25 and 28-31 are allowable if amended to conform to examiner's Group I and overcome the rejections of 35 U.S.C. §112, second paragraph. In view of the amendments to the claims, and for the reasons set forth below, it is submitted

that these claims are in a condition for allowance.

First, the claims have been amended to conform in scope to the examined subject matter.

Second, claim 1 and claims depending therefrom stand rejected under 35 U.S.C. §112, second paragraph, for failing to recite a 'therapeutically' effective amount. Claim 1 has been amended as suggested by the examiner, and, accordingly, this rejection under 35 U.S.C. §112, second paragraph, has been overcome.

Third, claims 1, 8, and 19 stand rejected under 35 U.S.C. §112, second paragraph, for failing to recite 'or' prior to the term 'prodrug.' In view of the amendment to claims 1, 8, and 19, it is submitted that this rejection has been overcome and should be withdrawn.

Fourth, claims 1, 8, 19, and 28-30 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite with respect to the variable W and substituents on W. It must be noted that the definition of W in claims 1, 8, 19, and 30 is clear, i.e., W is pyrazinyl. Amended claims 28 and 29 recite compounds wherein W is pyrazinyl.

With respect to optional substituents on W, applicants respectfully traverse the rejection. In particular, applicants respectfully submit that it is not necessary to restrict the scope of the claims by specifying the ring size, number of heteroatoms, or connecting point to 'the main core' in order to satisfy 35 U.S.C. §112, second paragraph. As set forth in the M.P.E.P.

at §2171, the purpose of the 35 U.S.C. §112, second paragraph, requirement to 'particularly point out and distinctly claim' under is to define the metes and bounds of the subject matter that applicants seek to protect. Applicants respectfully submit that a person skilled in the art can readily ascertain whether a given compound falls within the generic formulae as presently claimed. As a nonlimiting example, the terms the examiner apparently objects to, e.g., 'heterocycloalkyl,' 'heteroaryl,' and 'aryl,' have well-established meanings in the art. Moreover, each of these terms is described in the specification, and the specification also provides nonlimiting examples. For example, a nonlimiting description of 'heterocycloalkyl' can be found in the specification at page 30, line 23 through page 31, line 2. For a description of 'alkylene,' see page 31, lines 9-15 of the specification. For a description of 'aryl' and 'heteroaryl,' see page 31, line 19 through page 32, line 23 of the specification.

The examiner also is reminded that claim breadth does not equate to indefiniteness (see M.P.E.P. §2174.04). Because one of ordinary skill in the art can readily determine whether a given compound would fall within a claimed generic formula, the present claims fully satisfy 35 U.S.C. §112, second paragraph. Furthermore, claim 9 has been amended, and no longer recites 'one or more,' with the understanding that the claimed cytokine, lyphokine, growth factor, or other hematopoietic factor can be administered alone or in any combination. Accordingly, it is submitted that this rejection under 35 U.S.C. §112 should be withdrawn.

Fifth, claim 19 stands rejected under 35 U.S.C. §119, second paragraph, for differing in scope from claim 1. Applicants respectfully traverse this rejection. In particular, claims 1 and 19 are both independent claims, and properly can differ in scope. Also, claim 1 recites a method and claim 19 recites compounds. As such, claims 1 and 19 are different classes of invention, and a difference in scope of the compounds recited in the compound and method claims is proper, if not typical. Further, *both* claims 1 and 19 recite 'solvates.' Accordingly, it is submitted that this rejection of claim 19 under 35 U.S.C. §112, second paragraph, should be withdrawn.

Sixth, claim 8 stand rejected under 35 U.S.C. §112, second paragraph, because of the recitation of 'treatment of a medical condition by chemotherapeutic or radiotherapeutic' means is 'silent about the condition(s), and specific radiotherapy as well as the specific chemotherapeutic treatment, [and] does not exactly say what is excluded.' Applicants respectfully traverse this rejection. It is submitted that claim 8 is proper as presented, and that no requirement exists from [sic] a claim to 'exactly say what is excluded,' or that a claim be limited with additional recitations of specific conditions, or radiotherapies or chemotherapies.

Claim 8 recites:

> 'A method of sensitizing cells in an individual undergoing chemotherapy or radiotherapy for a medical condition, comprising administering a therapeutically effective amount of a compound of formula (I) in combination with a

> chemotherapeutic agent, a radiotherapeutic agent, or a mixture thereof to the individual. . . .'

Claim 8, therefore, recites the objective of the claimed method, namely, sensitizing cells an individual undergoing chemotherapy or radiotherapy for a medical condition. The claim also recites a step to be taken in the method, namely, administering a therapeutically effective amount of a compound of formula (I) in combination with a chemotherapeutic agent, a radiotherapeutic agent, or a mixture thereof to the individual. The specification clearly discloses numerous chemotherapeutic agents and radiotherapeutic agents, and chemotherapeutic and radiotherapeutic agents are recited in dependent claims 14 and 15. In addition, persons skilled in the art are well aware of the identity of these and additional anticancer agents. Accordingly, applicants respectfully submit that claim 8 fully complies with 35 U.S.C. §112, second paragraph, and that this rejection of claim 8 should be withdrawn.

Seventh, claim 14 stands rejected because of a recitation of chemotherapeutic agents, but a failure to state what is excluded from such recited chemotherapeutic agents. For the reasons set forth above, it is submitted that this rejection is in error and should be withdrawn. It is not applicants [sic] duty to describe what is excluded from the claims, but to clearly and particularly claim applicants' invention. It is submitted that the claims adequately and particularly recite the claimed subject matter, and that the specification provides sufficient guidance as to the metes and bounds of the claims. Accordingly, it

is submitted that claim 14 fully complies with 35 U.S.C. §112, second paragraph, and that this rejection should be withdrawn."

In summary, it is submitted that in view of the amendments to the claims, and for the reasons set forth above, pending claims 19, 21-25, and 28-31 comply with 35 U.S.C. §112, second paragraph, and are in condition for allowance.

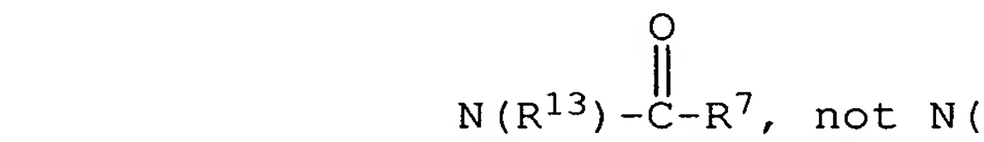
Claims 19 and 21 further stand rejected under 35 U.S.C. §112, second paragraph, for a difference in designation of the variables in the structure and in the definition. In view of the amendment to the structure in claim 19, it is submitted that this rejection has been overcome. The structure presently recited in claim 19 is identical to the structure originally recited in claim 19.

Claims 19 and 21 stand rejected under 35 U.S.C. §112, second paragraph, because the point of connection of C_{1-3}alkylene-N-phthalimide to the remainder of the molecule is not indicated. In view of the amendments to claims 1, 8, 19, 21, and 39, which show that the point of attachment is at the C_{1-3}alkylene moiety, it is submitted that this rejection has been overcome and should be withdrawn.

Claim 19 stands rejected under 35 U.S.C. §112, second paragraph, based on the contention that the substituent "NC" recited for R^8, R^9, and R^{10} "is not possible." Applicants traverse this rejection. The moiety "NC" is well known in organic chemistry as an "isocyano" group. Applicants enclose pages from standard organic chemistry references showing the "NC"

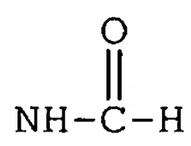
group and stable compounds having an "NC" group. Accordingly, it is submitted that the rejection is in error and should be withdrawn.

Claim 19 stands rejected under 35 U.S.C. §112, second paragraph, because of the recitation of $N(R^{13})COR^7$ for R^8, R^9, and R^{10}. The examiner contends that when R^7 and R^{13} are H, this group then is NH-C-OH, which is not possible. Applicants traverse this rejection. The examiner misread the substituent. The recited substituent is



$N(R^{13})-\overset{O}{\overset{\|}{C}}-R^7$, not $N(R^{13})-C-O-R^7$.

Thus, if R^7 and R^{13} both are H, the substituent is



$NH-\overset{O}{\overset{\|}{C}}-H$.

In addition, the substituent cannot be interpreted as the examiner contends because the carbon atom would have only two bonds. However, to clarify the claims, claim 19 has been amended to recite $N(R^{13})C(O)R^7$. Similar clarifying amendments were made in claims 1, 2, 5, 8, 10, 12, 25, and 30. Accordingly, it is submitted that this rejection should be withdrawn.

Claim 19 stands rejected under 35 U.S.C. §112, second paragraph, because of a recitation "when Q' is hydro." The examiner correctly points at that Q' cannot be hydro. Accordingly, claim 19 has been amended and the rejection has been overcome.

Claim 26 stands rejected under 35 U.S.C. §112, second paragraph. However, this rejection is moot in view of the cancellation of claim 26 from the application, without prejudice.

Claim 27 stands rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The examiner previously contended that the specification is enabling for treating rheumatoid arthritis, but not for treating cancer and other inflammatory conditions. Applicants respectfully traverse this rejection.

In practice, a physician diagnoses a cancer in an individual, and prescribes the proper treatment, either chemotherapeutic, radiotherapeutic, or both, to treat the cancer or other medical condition. In addition to this prescribed treatment, a compound of the present invention can be administered to the individual to *sensitize* cells to the prescribed treatment, and thereby render the treatment more effective.

According to the method claimed in the rejected claims, a Chk1 inhibitor is not administered alone to treat a cancer; another active agent is also administered. This is clearly set forth in claims 8-12, 14-18, and 27, each of which requires coadministration of a chemotherapeutic agent, radiotherapeutic agent, or both.

Accordingly, the claimed administration of a Chk1 inhibitor is *independent* of the cancer or prescribed treatment. The present compounds are not a "silver bullet" as previously contended by the examiner, but sensitize cells to treatment according to the recited method for the diagnosed cancer, regardless of

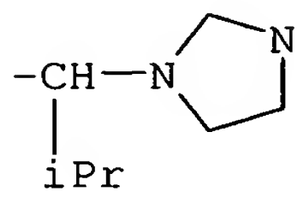
the cause or etiology of the cancer, or the body tissue afflicted by the cancer.

In addition, *all* method claims 8-12, 14-18, and 27 recite that the individual is being treated with a chemotherapeutic and/or radiotherapeutic agent. The individual may be suffering from any one of a variety of diseases, including inflammatory diseases, treatable with ionizing radiation (see specification, page 37, line 14 through page 38, line 2). In each case, the claimed use of a present Chk1 inhibitor *is in combination* with the primary chemotherapeutic and/or radiotherapeutic agent in order to sensitize cells to these agents.

Claims 19, 21-25, and 28-31 stand rejected under 35 U.S.C. §102(b) over various cited references. As set forth below, not one of the cited references anticipates the presently claimed compounds, and not one of the cited references is directed to inhibition of Chk1. The cited references, alone or in combination, also provide no motivation for a person skilled in the art to modify the disclosed compounds in a manner to arrive at the presently claimed compounds. Therefore, for the following reasons, it is submitted that the present claims are neither anticipated by, nor obvious over, the references cited by the examiner.

WO 99/11621 discloses thiourea compounds having a phenyl group substituted at the ortho position by $-CH_3$. In the presently claimed compounds, an ortho position of the phenyl ring is occupied by Q' which is OR^7, SR^7, or $N(R^7)_2$, and, accordingly, cannot be methyl.

WO 99/29674 discloses urea compounds having a phenyl group substituted at the para position by



Both ortho positions have a hydrogen atom. In the present claims, *one* of the phenyl ortho positions *must* be Q' as defined above. Q' cannot be hydrogen. Accordingly, the reference cited by the examiner cannot anticipate the present claims.

The compounds cited in the Heinisch et al. publication also cannot anticipate the present claims because the phenyl group of the urea compound has methyl and chloro as ortho-substituents. The present claims recite Q', as defined above, as an ortho substituent. Neither methyl nor chloro fall within the definition of Q'.

Similarly, the compounds disclosed in the second Heinisch et al. publication do not anticipate the present claims because Q' of the present claims does not encompass the methyl group substituent at each ortho position of the phenyl ring of the cited reference.

For the same reasons set forth above, an Atwal et al. publication cannot anticipate the present claims because the publication has an ortho t-butyl substituent on the phenyl ring. The present compounds cannot have a t-butyl ortho substituent when the other ortho substituent is H. The present claims require an ortho Q' group.

The compounds of the cited Wisterowicz et al. publication also do not anticipate the present claims because the compounds do not have a claimed Q' group. Both ortho positions of the phenyl ring in the cited reference either are unsubstituted or are chloro substituted.

The compounds of the cited Foks et al. publication do not anticipate the present claims for the same reason that the Wisterowicz et al. publication does not anticipate the present claims.

In view of the differences between the present claims and each cited reference, it is submitted that the anticipation rejection under 35 U.S.C. §102(b) should be withdrawn. It also is submitted that the present claims would not have been obvious to a person skilled in the art in view of the cited references, taken alone or in combination.

It is submitted that the claims are now in proper form and scope for allowance. Early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

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or H_2NNH_2, triazane for
, etc. are used. Names for
saturated carbon chains—*i.e.*,
NH, etc. Substituents may be

ane
iazanecarboxylic acid
yldiazene
enol
hyl-1-phenyltriazene
ne-2-phenyldiazane
lmethylene)diazane
iazene oxide

ranking functional groups are
ated ketones, thioketones, or
ontaining nitrogen chains for
included in Table 32.3.

l-1-propanone
diazanyl)phenylmethanethione
en-1-yl)-1-ethanimine

chain carries a positive charge
of diazane, triazane, etc. with
e word (*see* Chapter 24).

yldiazanium bromide

he nitrogen-containing groups
efix names as shown in Tables
ded names shown are to be
vever, some of those reflecting
any names in these Tables are
given in Chapter 13.

ficially to date to systematize
eral types of organic nitrogen
usage a large variety of class
evolved that severely taxes the
r alternatives these names have
ially recognized by the IUPAC
here constitute an attempt to
inciples of systematic organic

nomenclature so as to eliminate the need for many specialized names designating nitrogen-containing groups. In most cases one is urged to abandon such specialized names, as will be seen from Table 32.3.

Among the functional classes considered here, only those derived from the parent structures HOCN, HSCN, and HONC are properly named as acid derivatives. The officially approved inorganic names cyanic acid, isocyanic acid, and fulminic acid are retained as the basis for naming esters and organic anhydrides derived from these structures. Thus, although the 1970 IUPAC Inorganic Rules recognize isocyanic acid as the name for HNCO, the treatment as esters of structures in which the "esterifying" organic group is attached to *nitrogen* deviates from established principles and usage. Therefore, names such as "phenyl isocyanate" and "methyl isothiocyanate" are no longer recommended.

Table 32.1 Some Monovalent Nitrogen-Containing Substituting Groups (*No Longer Recommended)

Formula	*Prefix Name*
—OCN	Cyanato
—SCN	Thiocyanato
—ONC	Fulminato
—NCO	(Carbonylamino)
	*Isocyanato
—NCS	[(Thiocarbonyl)amino]
	*Isothiocyanato
—NC	(Carbylamino)
	*Isocyano
—NHCN	(Cyanoamino)
—N=C=NH	[(Iminomethylene)amino]
—NHOH	(Hydroxyazyl)
	(Hydroxyamino)
—NHSH	(Mercaptoazyl)
	(Mercaptoamino)
$-ONH_2$	(Azyloxy)
	(Aminooxy)
$-SNH_2$	(Azylthio)
	(Aminothio)
$-NHNH_2$	Diazanyl
	Hydrazino
$-NHNHNH_2$	1-Triazanyl
	*Triazano
—N=NH	Diazenyl
	*Diazeno
—NHN=NH	2-Triazen-1-yl

Members of the class RNC, properly called isocyanides, should be named substitutively. Radicofunctional names such as "phenyl isocyanide" are not recommended nor is the class name "isonitriles." Older

ods are applicable to the preparation of the dinitril
xample, may be prepared by $Br{\cdot}CH_2{\cdot}CH_2{\cdot}Br + 2\ NaC$
$+ 2\ NaBr$

ydrogen cyanide) may be prepared by the action of
allic cyanide: $NaCN + HX \rightarrow H{\cdot}CN + NaX$

$C_{14}H_{29}{\cdot}CN$ (m.p. 23) are liquids and are comparatively
They distil without decomposition. Hydrogen cyanide
ic form, HNC) is very poisonous and, in general, the
ric forms which are usually present, possess toxic prop

S REACT UNDER PROPER CONDITIONS:

) *hydrolytic,* (*b*) *reductive, or* (*c*) *simple, when following:*

$R{\cdot}CN + 2\ H_2O/H^+ \rightarrow R{\cdot}CO{\cdot}OH$ (acids) + NH_4^+

H $R{\cdot}CN + 4\ Na/4\ Et{\cdot}OH \rightarrow R{\cdot}CH_2{\cdot}NH_2$ (amines) $+ 4\ EtONa$

gent $R{\cdot}CN + R{\cdot}MgX \rightarrow R_2C{:}N{\cdot}MgX$, then
$R_2C{:}N{\cdot}MgX + H_2O/2\ HX \rightarrow R_2C{:}O + MgX_2 + NH_4X$

SO_4 $R{\cdot}CN + H_2O/(c.H_2SO_4) \rightarrow R{\cdot}CO{\cdot}NH_2$

$R{\cdot}CN + HX \rightarrow R{\cdot}C(X){:}N{\cdot}H$ (imide halides)

$R{\cdot}C(X){:}N{\cdot}H + HX \rightarrow R{\cdot}CX_2{\cdot}NH_2$ (amide halides)

fide $R{\cdot}CN + H_2S \rightarrow R{\cdot}CS{\cdot}NH_2$ (thioamides, poor yields)

HCl $R{\cdot}CN + CH_3{\cdot}CH_2{\cdot}OH/(\text{dry HCl}) \rightarrow R{\cdot}C(:NH){\cdot}OCH_2{\cdot}CH_3$

$R{\cdot}CN + R{\cdot}CO{\cdot}OH \rightarrow (R{\cdot}CO)_2N{\cdot}H$ (diamides)

$R{\cdot}CN + (R{\cdot}CO)_2O \rightarrow (R{\cdot}CO)_3N$ (triamides)

$R{\cdot}CN + NH_3 \rightarrow R{\cdot}C(:NH){\cdot}NH_2$ (amidines)

$R{\cdot}CN + R{\cdot}NH_2 \rightarrow R{\cdot}C(:NH){\cdot}NHR$ (alkyl amidines)

ıe $R{\cdot}CN + H_2NOH \rightarrow R{\cdot}C(:N{\cdot}OH){\cdot}NH_2$ (amidoximes)

n, when treated with metallic sodium in ether:

dry ether) $\rightarrow CH_3{\cdot}C(:NH){\cdot}CH_2{\cdot}CN$ (3-iminobutane-

ation is produced by sodium in the absence of ether,
idine derivative) results.

ylamines, Isocyanides or Isonitriles

s may be regarded as derivatives of the hydro-
e hydrogen atom has been replaced by the NC
be represented by the general formula R·NC.

The carbylamine test is used to identify the presence of primary amines, due to its sensitivity, the test has no quantitative value as secondary and tiary amines usually contain sufficient traces of primary amines to give a itive test.

The additive properties of the carbylamines (R·NC) indicate that bivalent bon may be involved in the linkage, but the most recent work has indicated they contain a triple covalent bond and one electrovalent bond. Methylylamine, for example, may be represented *electronically* by $H_3C{:}N{:}{:}C{:}$, ethanenitrile by $H_3C{:}C{:}{:}N{:}$. They are functional and dynamic (esially at elevated temperatures) isomers of the nitriles.

Nomenclature:

uctural Formulas	I.U.C. Names	Common Names
$I_3{\cdot}NC$	methylcarbylamine	methyl isocyanide
$I_2{\cdot}CH_2{\cdot}NC$	ethylcarbylamine	ethyl isocyanide
$I_2{\cdot}CH_2{\cdot}CH_2{\cdot}NC$	propylcarbylamine	propyl isocyanide
$(I_3)_2CH{\cdot}NC$	isopropylcarbylamine	isopropyl isocyanide

Preparations:

THE CARBYLAMINES MAY BE PREPARED:

1. *By the replacement of the halogen atom in an alkyl halide by the carbylamine group* (·NC):

a. $R{\cdot}X + Ag{\cdot}CN \rightarrow (R{\cdot}N{:}C\,[Ag]\,X) \rightarrow R{\cdot}NC$ (also, some R·CN) + AgX

b. $R{\cdot}X + NaCN$ (or KCN) $\rightarrow R{\cdot}NC$ (but mostly R·CN) + NaX

2. *By the action of chloroform, in the presence of alcoholic sodium or potassium hydroxide, on primary amines* (*Hofmann carbylamine reaction*):

$$R{\cdot}N\begin{bmatrix} H & Cl \\ & + \\ H & Cl \end{bmatrix} C \begin{bmatrix} H \\ \\ Cl \end{bmatrix} + 3\ NaOH,\ alc. \rightarrow R{\cdot}NC + 3\ NaCl + 3\ H_2O$$

D. Physical Properties:

The alkylcarbylamines are colorless liquids which distil without decomposition. They are slightly soluble in water, but readily soluble in alcohol and ether. They possess a very disagreeable odor and are quite poisonous.

E. Chemical Properties:

THE ALKYLCARBYLAMINES REACT UNDER PROPER CONDITIONS:

1. *By addition,* (*a*) *hydrolytic,* (*b*) *reductive,* (*c*) *simple, or* (*d*) *oxidative, when treated with the following:*

a. Excess H_2O/180°C.	$R{\cdot}NC + 2\ H_2O \rightarrow R{\cdot}NH_2$ (primary amine) + $H{\cdot}CO{\cdot}OH$
b. $Na/CH_3{\cdot}CH_2{\cdot}OH$	$R{\cdot}NC + 4\ Na/4\ Et{\cdot}OH \rightarrow R{\cdot}NH{\cdot}CH_3$ (sec. amine) + $4\ Et{\cdot}ONa$
c. 1. Grignard reagent	$R{\cdot}NC + R{\cdot}MgX \rightarrow R{\cdot}N{:}C\,(R){\cdot}MgX$, then $R{\cdot}N{:}C(R){\cdot}MgX + H_2O/HX \rightarrow R{\cdot}NH_2 + R{\cdot}CHO + MgX_2$